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## A Brief Perspective on the Early History of American Infectious Disease Epidemiology

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The early history of epidemiology is closely linked to the history of infectious diseases and can be divided into three distinct periods. The earliest period, which can be traced to the writings of Hippocrates in the third and fourth centuries B.C., was that of clinical description of diseases with little investigation into their specific characteristics and etiologies. The second period, spanning the eighteenth and nineteenth centuries, may be distinguished by the rejection of early Hippocratic and Galenic doctrines and the more systematic description of morbid conditions. The third period, which was marked by the discovery of specific microbial causes of disease, spurred an extraordinary growth of knowledge and scientific exploration. This period will be the main focus of the paper, as it had the greatest influence on the development of American infectious disease epidemiology.

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It is a pleasure to dedicate these few remarks to Alfred Evans, who has been the quintessential academic: teacher, virologist, epidemiologist, author, philosopher, and constructive critic. I am proud to number him among my friends.

Epidemiology, emerging from the study of infectious disease, became a field for scientific study out of empirical necessity. Accordingly, any sketch, however brief, of the history of infectious disease epidemiology in the United States or elsewhere is necessarily intertwined with the profound effect of infections on social organization, culture, religion, and virtually every aspect of daily life. To attempt an overview of such a broad canvas requires a treatise far beyond the desires of the organizers of this symposium, or of the capabilities of this reviewer. Instead I shall sketch briefly a few formative influences on the development of American epidemiology. I shall make no attempt to review the dependence of American thought on advances being made in France, Britain, and, later, in Germany, despite its importance.

The history of infectious diseases can be conveniently divided into three broad phases [1]. The earliest phase, such as appears in the Hippocratic treatises, was that of clinical description with relatively few specific preventive or therapeutic measures. The second, occurring mainly during the eighteenth and nineteenth centuries, was the time when the early Hippocratic and Galenic doctrines about fever and disease that had dominated medical thought for centuries were being overthrown. The ancient doctrines held that disease was a consequence of imbalance between natural forces within and outside the body, and therapy was directed toward restoring this balance. Thus, separating fevers and other diseases into distinct nosologic entities was a relatively pointless exercise, except for broadly descriptive and prognostic purposes. Although a

few specific descriptions of disease can be extracted from the writings of Boerhaave and Sydenham, it was not until the eighteenth and nineteenth centuries that the more systematic descriptions of disease were presented.

In the same period, another major event was taking place that is still only dimly understood. Increasing prosperity, better food and housing, and changing living conditions brought the first major downward trends in overall mortality. These quite revolutionary societal advances created the impression that medical care accounted for the improving health, a view that few physicians wished to dispel, and that most believed, in accordance with the concepts of therapy of the time.

The third phase, characterized by the logarithmic growth of knowledge and of scientific exploration, was a period that received its greatest stimulus from the discovery of specific microbial causes of disease by Pasteur and Koch, which blossomed into the present era of scientific exploration of disease.

In the colonial and postcolonial periods, American medical science was mainly derivative, and bright young Americans ventured to Britain, France, Holland, and elsewhere on the European continent to seek advanced training. Empiricism was the essential theme. The settlement of virgin territories, the requirements of establishing an agricultural and commercial basis for continued existence, and the political turmoil that accompanied these aspirations permitted little opportunity for scholarly reflection or observation.

Most medicine in the colonies, as in Europe, was practiced by empirics, sometimes with training as apothecaries, usually products of apprenticeships of varying length and standards. Most practitioners of medicine had other occupations, such as that of clergyman or bookseller. University training was rare, and most medical ideas were imported. What did not need to be imported was the vision of new opportunity and the philosophical view, made necessary by the thrust and the success of colonization, that the environment was controllable. This view spread to disease as well as to the rigors of daily production of food, acquisition of shelter, and other functions of daily life.

When Jenner's vaccine was brought to the young nation, its introduction was accompanied by business acumen and uncertainty as to its value. Indeed the practical hardheadedness of the political leaders of the time and their doubts about the safety and efficacy of the vaccine led to a clinical trial. To tell this tale requires some background about immunization against smallpox in the colonies and during the decades after independence.

Inoculation for the control of smallpox was an early importation from England, where its use had been expanding for years. Governor Winthrop, Zabdiel Boylston, Cotton Mather, and many others led the stalwart band who were convinced that inoculation was a useful procedure, despite the tragedies that sometimes followed its use, tragedies that led to fierce opposition to the procedure.

After Jenner's discovery was announced, the first lymph from cowpox lesions was obtained by Benjamin Waterhouse. Controversy concerning its value came from three major sources: those who feared and opposed variolization, those who supported variolization and were uncertain that cowpox would confer immunity to smallpox, and those who objected to Waterhouse's method of commercial exploitation of Jenner's material. The political leaders of the Boston community resolved the arguments by performing one of the first controlled clinical trials in American history.

The scene in which this trial was conducted has been described by Blake [2]. Waterhouse, born a Quaker, but apparently not a practicing Friend, was in close

communication with co-religionist John Coakley Lettsom, the London physician who followed in the footsteps of John Fothergill's reformist practices. Lettsom, in 1799, sent Waterhouse a copy of Jenner's "Inquiry. . . ." The young, newly appointed first Professor of Physic at Harvard University, published, on March 16, 1799, a summary of Jenner's discovery in the *Columbian Centinel*, a Boston newspaper. Soon thereafter, Waterhouse successfully vaccinated his son, and then members of his household. Waterhouse was promptly overwhelmed by requests for the material, and he evolved a method of dispensing it that brought a storm of controversy. He chose to share the precious vaccine only with selected physicians who promised to return a fraction of their profits from the use of the vaccine to the academic entrepreneur. Waterhouse claimed that in this manner he could control the quality of the lymph that was being used for vaccination; however, his testy personality, the accumulating monopolistic profits, and the failure of some of the cowpox lymph to produce the lesions that signified protection, caused the method to come into some disrepute.

Waterhouse's motivation for tight control was not entirely self-serving. Few practitioners heeded his careful strictures about which lymph was proper to use and which was not (for example, cloudy or malodorous lymph was not to be used), so vaccination often failed to produce the local lesion that signified success, and sometimes produced severe secondary infections. In one catastrophic incident in Marblehead, Massachusetts, the cowpox material was mixed with smallpox exudate and an epidemic followed, adding to the fear and uncertainty about the new procedure.

Waterhouse did set up facilities for providing the poor with free vaccine, and he advocated a system of Vaccine Institutions in Boston for dissemination of vaccination free of charge, but he and his procedure had become controversial enough to cause the idea to languish. In 1801, however, Waterhouse provided President Thomas Jefferson with free vaccinia material despite Jefferson's stated misgivings about monopolies being operated for profit.

As interest, apprehension, and skepticism grew, and smallpox was still a menace to the community, Waterhouse pressed the Board of Health of Boston (the first in the country, founded in 1779 and chaired by Paul Revere) to perform a critical experiment. The Board sought the advice of prominent physicians and on May 31, 1802, agreed to proceed with a controlled trial. The experiment began on August 16 with twenty vaccinated volunteers. A temporary hospital was set up on the relatively deserted Noddle's Island, now East Boston, and thirteen of these vaccinated young men were housed there, along with two unprotected individuals. All fifteen were housed in one room. All received fresh smallpox material that was obtained from a practitioner of variolization in Falmouth, on Cape Cod. The two unvaccinated boys became ill, and the thirteen previously vaccinated boys remained well. Then the entire vaccinated group, this time including the remaining seven, were again inoculated with infectious material and housed in the same room with the two boys who were recovering from smallpox. No new cases appeared, and the experiment was declared a success for vaccination. Thus was a skeptical medical and lay public convinced and vaccination spread across the new nation.

In France, the Royal Academy of Medicine from its inception was charged with the responsibility for conducting controlled trials of the effectiveness of medicines and medical procedures, but the development of this mandate was frustrated by the political revolution. Mathematicians in France and in England had begun to formulate

statistical theories, however, and practical observers, such as P.C.A. Louis, had begun systematic collections of clinical data [3,4].

Statistical maturation in Britain, spearheaded by Benjamin Gompertz and Thomas Rowe Edmonds, applied and extended by the remarkable William Farr [5], made it inevitable that Americans would follow. Even before these important events in Britain, however, Dr. Edward A. Holyoke had begun to investigate the relation of death to diseases that caused it. The American Academy of Arts and Sciences, founded by John Adams to demonstrate that Philadelphia was not the sole center of learning, had published “regular and uniform Bills of Mortality from the several towns within the Commonwealth” in 1785. Holyoke calculated longevity from data supplied by sixty-two towns in Massachusetts and New Hampshire and showed that life expectancy at age 65 was almost 12.5 years—a remarkable testimony to the relatively healthful colonial environment, with its lack of crowding, reasonable food supply, and rare urban squalor [6]. Science was not a major preoccupation of the new nation, however, despite the contributions from a small number of gifted persons endowed with the intellect and the leisure to produce scientific information. Most of what was known in science and medicine continued to flow from Europe.

By the middle of the nineteenth century, enough information had accumulated in the major American cities, and enough young medical practitioners had studied in Europe, to be able to combine European teachings with their own perceptions, and criticisms as well as embellishments on European practices were beginning to appear. Particular concerns were the lack of humanitarianism in French hospitals and the lack of evidence of therapeutic effectiveness in practice in general [7]. From a scientific viewpoint, only Oliver Wendell Holmes’s analysis of the contagiousness of puerperal fever stands out, not only because of the careful marshalling of evidence, but also because of his use of probability estimations that were reflective of the advanced statistical thinking of the time [8].

The burst of knowledge that was ushered in by the first demonstrations of microbiologic causes of disease had its counterparts in scientific research in the States, but only a few contributions were of sufficient quality to have altered epidemiologic thought. Although Austin Flint had written in compelling fashion in 1874 of the “Logical Proof of the Contagiousness and non-Contagiousness of Diseases,” the first discussion of bacteria in the American literature was a review by L.A. Stimson, in the *New York Medical Journal* (in which Flint’s article had appeared a year earlier), with a briefer version in *Popular Science Monthly* [9]. Two years later, in 1877, two articles in the *Boston Medical and Surgical Journal* summarized Lister’s epochal work on antiseptic surgery and gave details of its successful application to a small number of patients in the Massachusetts General Hospital [10,11]

Thomas J. Burrill was probably the first to introduce bacteriology into the university curriculum. In 1880, Burrill published his observations on *Micrococcus amylovorus* as the cause of pear blight, satisfying what later became the Henle-Koch postulates about etiology. He had introduced bacteriological study into his course on botany at the University of Illinois, probably a year or two before announcement of his discovery [12]. Burrill became an example of extinction by promotion; he assumed increasing administrative responsibility and ultimately the presidency of the University.

In medicine, William Henry Welch at Bellevue Medical College and T. Mitchell Prudden at Columbia set up bacteriological laboratories in New York City, with foundation help. By 1885, when Welch moved to Johns Hopkins, he could report that

twenty-six medical graduates were working in his laboratory. Several original investigations, including his own and those of George M. Sternberg, who had been permitted by the Army and by Hopkins to work in Welch's laboratory, reached the standards of similar research in Europe.

Daniel E. Salmon began his work in the Division of Animal Industry of the federal government in 1879, was named chief of the renamed Bureau in 1884, and promptly took on a promising young man from Albany, Theobald Smith. Smith had received a state stipend to attend Cornell and had received his M.D. in 1884, supplementing his scholarship as a church organist. At age 25, Smith was named director of the pathology laboratory in the Bureau, where he remained for five years, and was professor of bacteriology at the then Columbian (now George Washington) University in Washington, D.C. Salmon and Smith isolated the organism of hog cholera, now *Salmonella cholerae suis* [13], following this work by the demonstration that the attenuated bacteria conferred immunity to the disease, providing a major new principle in the control of disease [14].

Thus did Theobald Smith begin a career marked by most important microbiologic and epidemiologic discoveries. For all the adulation that he has received, it still seems inadequate; he did not receive the Nobel prize when lesser discoveries were so recognized. Smith came to Harvard in 1895 to be the first George Fabyan Professor of Comparative Pathology and to direct the Antitoxin and Vaccine Laboratory of the Massachusetts Board of Health. He remained there for twenty years until he moved to the Rockefeller Institute, as Director of the Department of Animal Diseases in Princeton, New Jersey.

In 1889, Smith published his first observations on cattle fever, and in 1893 published, with the veterinarian, F.L. Kilborne, his monumental work entitled *Investigations into the Nature, Causation and Prevention of Texas or Southern Cattle Fever* [15]. This devastating disease, which was producing serious economic effects on the cattle industry, had been observed by keen cattlemen and scientists, and a few of these observations were agreed upon. Clinically, the disease was characterized by high fever, sometimes to 109°F., with severe anemia and hemoglobinuria. At autopsy there was often severe disease of the liver as well. Etiology was unknown.

Smith argued that there were only three etiologic possibilities. First, the disease might be a disease of the liver with destruction of the blood due to absorption of bile. Second, the disease might be due to a germ in the intestinal tract that secreted a ptomaine (this was the time when ptomaine poisoning seemed a reality) and the ptomaine caused the destruction of the blood. Third, the disease might be due to an organism that lived in the blood and destroyed the red cells. By 1886, he had, by making imprints of the spleens of cattle dying of the disease, seen within or on the erythrocytes "small round bodies perhaps  $1\mu$  in diameter. . . . It took four years of slavery at the microscope, at autopsy, at watching ticks hatch from the egg . . ." to solve the problem and to demonstrate the first arthropod-borne infection in medical history. He had drawn on many earlier empirical observations in deciding the direction of his research, and he spelled out the epidemiologic information that indicated the directions he had selected for his intensive studies:

- a. Southern cattle that bore the infection were generally free of the disease;
- b. Infection was carried during the warm season—Southern cattle were harmless during the winter;

c. Transmission from Southern to Northern cattle was not direct, in that ground over which Southern cattle had passed could, if Northern cattle grazed there even weeks later, still transmit the disease;

d. Southern cattle, after a short time in the North, lost their ability to transmit the disease;

e. Northern cattle with the disease did not transmit the disease to other Northern cattle but Northern cattle brought South contracted the fever.

Salmon drew a map delineating the geographic distribution of the disease, which occurred south of the thirty-seventh parallel, except along the eastern slope of the Allegheny mountains where it crept up to a line between the thirty-eighth and thirty-ninth parallels.

Smith, having observed the bodies in the red cell, and suspecting the tick as the reasonable vector that would put together the epidemiologic patterns, enlisted the collaboration of Kilborne, an expert on the tick, and they transmitted the disease by putting recently hatched ticks on susceptible cattle. They described the disease produced during their experiments, providing a comprehensive listing of the symptoms and signs, laboratory findings, pathologic changes, and seasonal fluctuation of the disease. Smith suggested that cover slips were the best way to look at the blood, and included a diagram showing how cover slips could spread a small drop of blood on their surfaces—a method that students, house officers, and hematologists have used without realizing that it originated in the study of cattle fever before the twentieth century. The dried blood films showed the organism in various stages within the red blood cells, and the paper has beautiful and complete color plates as well as black-and-white drawings. The suggested name of the organism, not yet cultivated, was *Pyrosoma bigeminum*, now *Babesia bigemina*, because of its bipolar appearance and its association with the fever. Smith related his findings to Lavarán's recent discovery of pigmented forms in the red cells of malarial patients, implying that arthropods should be sought in the latter disorder, but indicating that his organism differed in its appearance from the malarial parasite by the absence of pigment, as well as in other morphological details. The tick that carried the parasite, *Boophilus bovis*, later *Ixodes bovis*, and now *Boophilus annulatus*, was studied during its entire life cycle. Its fertilization on the cattle after feeding with blood, the manner in which the females dropped to the ground, the wintering of the organism on the skin or in the ovum in the ground were all described. A worldwide survey of the disease showed it to be present in Africa, Romania, and other countries.

There was little left to be said after the paper was published, other than to admire a presentation that is close to being unmatched in medical history for its completeness and accuracy. The weaving together of epidemiologic observations to create the hypotheses, of controlled trial to test these, of laboratory and clinical observation to uncover etiology and methods of control, and extension of the findings to other diseases such as malaria, was a scientific achievement as elegant as it is disciplined. Within the decade, the transmission of malaria and yellow fever by mosquitos was proven.

Smith did not stop here, although this work guaranteed medical immortality for him. He observed anaphylaxis in guinea pigs that had been given diphtheria antitoxin followed later by a slightly larger dose of the same serum. He transmitted this discovery to Paul Ehrlich in a letter, and some years later Ehrlich's student, Otto, published a detailed analysis of what he called the Theobald Smith phenomenon, or

anaphylaxis. Smith differentiated for the first time the human from bovine tubercle bacilli, paving the way for the demonstration of bovine tuberculosis and its control, and he also studied sarcosporidae, tracing the life cycle of these parasites from murine host to murine host by direct feeding of infected muscle. Perhaps as much as any accomplishment, since he was an unabashed and unapologetic utilitarian, he took pride in having produced a high-quality diphtheria antitoxin for the Massachusetts population, having increased production efficiently and economically, and in having supplied the life-saving serum for 10 percent of its commercial cost.

The development of our knowledge of infectious disease in the United States and the attendant growth of epidemiologic theory and practice demanded institutional and governmental responses to the lessons that were accumulating. The first federal and state hygienic laboratories in the U.S. were established in 1887, reflecting not only an increasing awareness of the American scientific community but also the evolving political attitude that the protection of the public health should be addressed through governmental support. The first municipal laboratory was established in 1888 in Providence, Rhode Island, and by 1914 all states except Wyoming and New Mexico had public health laboratories. The first federal hygienic laboratory began operations in one room of the Marine Hospital on Staten Island in 1887 under the direction of Joseph James Kinyoun, and in 1901 Congress designated thirty-five thousand dollars for this Hygienic Laboratory, providing the first federal mandate for the investigation of "infectious and contagious diseases, and matters pertaining to the public health" [16]. Over the next forty-three years, this one-room bacteriologic laboratory evolved into the National Institutes of Health (NIH), formally established by Congress in 1930 [17]. Other organizational entities developed concurrently with NIH. For example, the American Public Health Association, founded in 1873, had its laboratory Section in 1901, with Theobald Smith as its chairman. Numerous related societies and their journals followed.

The close interrelationship between clinical and public health practices, laboratory investigations, and governmental actions is illustrated better in the case of infectious diseases than with any other category of disease. This interrelationship provided models for students of many chronic diseases.

Epidemiologic techniques, moving from their roots in infectious disease, have become necessary for the most efficient and acceptable solutions to major problems in chronic disease, health care, hospital management, and innumerable other problems. Infectious disease epidemiology has resurfaced with the recognition of new hitherto unobserved infectious diseases. Legionnaire's Disease, toxic shock syndrome, acquired immunodeficiency syndrome, and many other illnesses have demonstrated the importance of basic, time-honored epidemiologic methods in the understanding of disease. These methods, refined and sharpened as they inevitably will be, are certain to be essential for further understanding the natural history of diseases, for the evaluation of therapeutic and prophylactic measures, and therefore for the advancement of the public health.

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